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Review Article

Innovative Approaches in Combating Antimicrobial Resistance: A Comprehensive Review

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Abstract:
Antimicrobial resistance (AMR) is a significant and growing hazard to worldwide public health, caused by antibiotic overuse and misuse, as well as a lack of innovation in pharmaceutical research. This thorough study investigates novel techniques to combating AMR, such as combination medicines, immunotherapy, phage therapy, antimicrobial peptides, nanoantibiotics, probiotics, CRISPR-based therapeutics, and antimicrobial photodynamic therapy. These tactics use cutting-edge technologies and innovative mechanisms of action to overcome resistance and improve therapeutic efficacy. Antimicrobial treatment regimens can be optimized and resistance development can be minimized by the integration of combination drugs and personalized medicine. However, tackling the difficulties of AMR necessitates a multidisciplinary and collaborative effort involving healthcare practitioners, researchers, legislators, regulatory agencies, and the pharmaceutical sector. By embracing innovation, teamwork, and proactive measures, we can reduce the burden of AMR and ensure antibiotics' continued effectiveness for current and future generations.

Keywords: Antimicrobial resistance, Combination therapies, Immunotherapy, Personalized medicine, Crispr-based therapies.

Introduction

The development of antibiotics to treat infectious infections has had a significant impact on animal and human health since the 1940s. However, the careless use of disinfectants and antibiotics has led to previously unheard-of global health issues. This problem arose when bacteria started to generate genes that allow resistance to antibiotic residue. Resistance genes make it possible for infections to flourish in a range of conditions, which limits the options for treating infectious diseases and raises morbidity and mortality by causing a large number of bacteria that are resistant to medications to grow in both humans and animals.

Antibiotic resistance brought on by ESKAPE infections has been linked to increased risk of morbidity and mortality, which has increased the financial burden, especially in intensive care units in developing nations [1]. The problem is exacerbated by the sluggish pace of antibiotic development [2,3]. By 2050, drug-resistant bacteria are predicted to cause 10 million deaths annually instead of just 700,000 [4]. Laxminarayan et al., (2016) claim that the nation that uses antibiotics the most has produced an environment that is conducive to drug-resistant diseases. Major contributions to the issue include low public health conditions, a high infection incidence, a lack of public awareness of drug-resistant bacteria, inexpensive availability to antibiotics, and the careless administration of these medications [5].

The development of new antimicrobial drugs, semisynthetic derivatization of current antibiotics, searching for antibiotic substitutes, and boosting the effectiveness of current antibiotics are currently the approaches used to combat bacterial antibiotic resistance. It is still challenging to produce novel antibiotics with specific targets, especially against gram-negative bacteria, even with the FDA's recent clearance of new antibacterial drugs [6]. Additionally, the spread of resistance microbes is far faster than the discovery of new antibacterial drugs [7]. Any treatment that relies only on antibacterial mechanisms will eventually cause bacteria to become resistant, and substantial

resistance might appear in the months or years following the introduction of a new antibiotic into clinical use [8]. There aren't many effective alternatives to antibiotics that can completely replace them, despite intensive efforts to find them. Even now, the first line of treatment for diseases in humans and animals is still antibiotics. In light of the current problems and limitations, investigating new approaches to boost the effectiveness of currently available antibiotics could be a worthwhile endeavour. Antibiotic-resistant bacteria are thought to be combatable with combination therapies [9,10]. The adoption of combination therapy as a therapeutic approach for MDR infections is supported by the possibility that the combined stress is more effective than each one alone. Antibiotic-antibiotic, non-antibiotic-antibiotic, and antibiotic-non-antibiotic combinations are some examples of these combinations [11]. Certain combinations of antibiotics have been scientifically tested and proven to be effective; one such combination is Trimethoprim-Sulfamethoxazole, which was licensed for usage many years ago. But this combination may expose patients to more unneeded antibiotics while they're being used, which could lead to the development of bacterial resistance [12]. The field of non-antibiotic-non-antibiotic combos is unexplored. Moreover, it is unclear how effective the two non-antibiotic chemicals will be as a treatment in vivo, especially when complicated bodily fluids are present [12]. Therefore, combining antibiotics with non-antibiotic compounds is the most viable strategy. The potential of this combination is demonstrated by the efficacy of amoxicillin/clavulanate potassium [13]. This non-antibiotic formulation showed little to no antibacterial action when administered on its own, but it greatly increased its activity when combined with antibiotics. This strategy holds a lot of promise because it can lower the usage of antibiotics, stop the emergence of resistance, and thereby increase their effectiveness.

Mechanisms of Antibiotic Resistance in Bacteria

Studies have shown that bacterial evolution is the cause of bacterial drug resistance [14,15]. Before antibiotics were discovered, there were genes that made bacteria resistant to medications. At the moment, extrachromosomal mobile elements or chromosomes are the mechanisms mediated by bacterial antibiotic resistance. Numerous processes, such as drug modification and destruction, target area changes, decreased intracellular accumulation of antibiotics, and alterations in bacterial metabolic status, might lead to the establishment of antibiotic resistance (Figure 1). For the purpose of developing novel strategies to prevent or reverse bacterial resistance, it is imperative to comprehend the process underlying bacterial resistance [16,17].

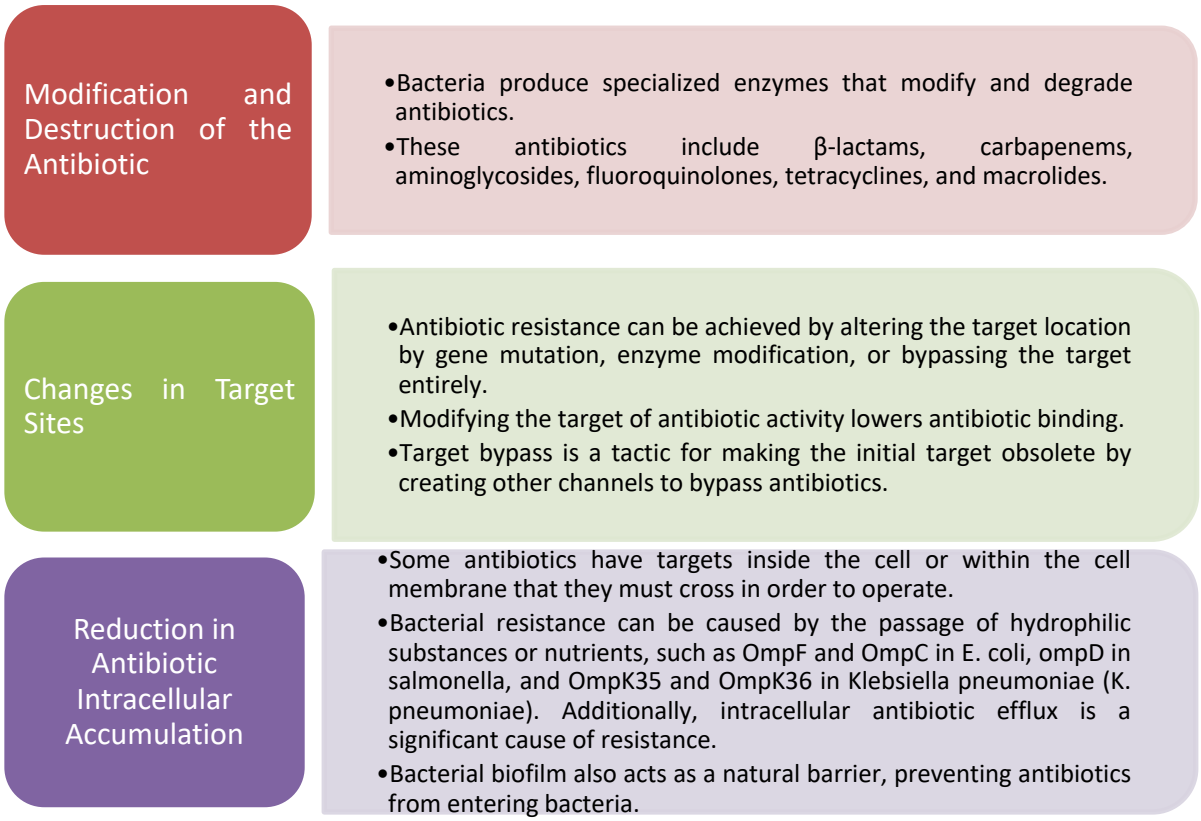

Figure 1: Overview of the molecular mechanisms of antibiotic resistance

The Situation of Antibiotic Resistance Right Now

The emergence of multidrug-resistant bacteria that can withstand the effects of last-resort medicines like tigecycline and colistin is a result of the recent rise in resistance to widely used antibiotics. According to a WHO assessment on the worldwide shortage of novel antimicrobials, which was released in April 2021, currently approved medications and the present pipeline for antibiotic development are insufficient to combat drug-resistant bacteria [18]. The study looks into medications that are currently in clinical development to treat conditions included on the bacterial priority pathogens list from February 2017.

In its analysis, which looked at 27 such agents such antibodies and bacteriophages [19], the WHO for the first time included non-traditional antibacterial medicines. Additionally, in its annual report on the Antimicrobial Resistance Research and Surveillance Network (January 2020–December 2020), the Indian Council of Medical Research (ICMR) [20] disclosed current developments in resistance to important infections in India. Drug-resistant bacteria, including those resistant to cephalosporins, carbapenems, and monobactams, and β-lactam— β-lactamase inhibitors—are become less vulnerable to frequently used antibiotics, according to data from tertiary hospitals and research labs. Since the COVID-19 pandemic struck India during the reporting period, isolates from secondary bacterial infections in individuals who tested positive for the virus were also analyzed for resistance patterns.

These results showed that Klebsiella pneumoniae (K. pneumoniae) was the most frequently isolated pathogen from the respiratory tracts of COVID-19-positive individuals, followed by Acinetobacter baumannii (A. baumannii) and Escherichia coli (E. coli). Moreover, these bacteria exhibited a significant increase in antibiotic resistance when they were isolated from COVID-19-positive patients. In addition, a recent study conducted in the United States by the Centers for Disease Control (CDC) revealed that an estimated 2.8 million people are infected with antibiotic-resistant bacteria annually, leading to 35,000 fatalities. Moreover, $4.6 billion is spent on treating infections brought on by six drug-resistant bacteria. Based on their potential threat to human health, the CDC has categorized 18 antibiotic-resistant bacteria and fungi into three categories: "urgent, serious, and concerning" [21]. In light of these conditions, the development of innovative therapies for bacterial infections brought on by pathogens resistant to multiple drugs is critically needed.

Drug resistance is a continuous process

Microorganisms are incredibly intelligent and rapidly adapt to new settings in order to survive and flourish. Antibiotic resistance was first ignored since it was not a pressing concern, even though it appeared soon after antibiotics were employed clinically. Penicillin-resistant Streptococcus pyogenes was discovered in the 1940s, although sulfonamide-resistant S. pyogenes first surfaced in human clinical settings in the early 1930s. It was discovered in the 1950s [22] that bacteria were becoming more resistant to drugs.

Two main pathways are thought to be involved in the development of antibiotic resistance: horizontal evolution (acquisition of inheritable antibiotic resistance genes from other bacteria via conjugation, transduction, or transformation) and vertical evolution (mutations that cause antibiotic tolerance that can be transmitted to offspring). Horizontal gene transfer is a crucial pathway for the spread of antibiotic-resistant genes among bacteria, according to a comprehensive genomic analysis of diseases in humans and animals [23]. Despite being a serious problem, antibiotic resistance was long disregarded [24].

The identification of bacteria that produce resistance to penicillins and cephalosporins, such as XDR Mycobacterium tuberculosis, Multidrug-Resistant Acinetobacter baumannii, Enterobacteriaceae, Neisseria gonorrhoeae, and Pseudomonas aeruginosa [25], worries biochemists and clinicians. Ten years ago, a patient who was admitted to a hospital in New Delhi, India [26], had a single strain of Escherichia coli and Klebsiella pneumonia that tested positive for the New Delhi metallo-b-lactamase 1 (NDM-1). The majority of disease burden is caused by E. Coli infections resistant to third-generation cephalosporins, of which more than half are found in the community. This suggests that antimicrobial stewardship, including prescribers and interventions, should reach beyond of hospitals and into the primary care system in order to lessen the burden of antimicrobial resistance (AMR) [27].

The Use of Antibiotics and Its Effects

The idea that using antibiotics on people or animals is safe has evolved. Antibiotics harm both humans and animals in addition to eliminating microorganisms. Although extensive scientific testing on their safety and effectiveness has led to recommendations for their use in humans, antibiotics nevertheless present health hazards to humans when it comes to bacteria. Regulating agencies and medical professionals are worried that prolonged use of some antibiotics may have detrimental effects on a person's health [28].

For instance, doctors all around the world prescribe fluoroquinolones since they are generally safe for patients. Medical professionals and regulatory agencies have been pushed to reconsider the usage of antibiotics in veterinary and biomedical settings due to their shocking negative effects. Antibiotic side effects are powerful instances of what drugs may do to individuals besides treating infections. These include mitochondrial toxicity, neuropsychiatric issues, and damage to muscles and tendons. Although challenging to treat, fluoroquinolone-associated disability (FQAD) is not very successful. It is advised that antibiotics be administered only for critical conditions due to the recurrent cases of FQAD [28]. A brief summary of the many risks associated with the usage of antibiotics may be found in Table 1.

Table 1: The potential consequences of antibiotic usage

Consequence	Description
Antibiotic Resistance	Antibiotic overuse and misuse can result in antibiotic-resistant microorganisms.
Disruption of Microbiome	Antibiotics can kill beneficial bacteria in the stomach and disturb the balance of the microbiome.
Allergic Reactions	Some people may have allergic reactions to antibiotics, which can range from mild to severe.
Secondary Infections	Antibiotics can occasionally result in secondary infections, such as yeast infections or Clostridium difficile.
Impact on Immune System	Prolonged or regular antibiotic use may reduce the immune system's ability to fight infections naturally.
Drug Interactions	Antibiotics may interact with other drugs, lowering their effectiveness or producing adverse effects.
Environmental Impact	Antibiotics excreted by humans and animals can contaminate the environment and contribute to antibiotic resistance.

Immunotherapy

Immunotherapy is not a novel concept, but it is now a very attractive treatment option due to the discovery of highly specific human polyclonal or monoclonal antibodies that can target a wide range of biological locations. Adjuvanted, multieptitope bacterial vaccines for active immunization as well as monoclonal and polyclonal antibodies for passive treatments against bacterial illnesses are being developed [29]. Transchromosomic cattle have been produced to produce large numbers of excellent human polyclonal antibodies against bacterial and viral antigens [30]. Monoclonal antibodies can be engineered with favorable properties and half-lives that enable them to opsonize bacteria or inhibit virulence factors in the absence of antibiotics [31]. Immune adjuvants are being developed for therapeutic purposes to increase the host's cellular and humoral adaptive immunity [32]. A wide range of adjuvants, including interleukin-7, granulocyte macrophage colony stimulating factor, and programmed cell death ligand-1 antibody, are being studied. Immunotherapy with adjuvants such as these may be beneficial for patients with sepsis-induced immune suppression [32].

Phage Therapy

Despite a number of challenges, the use of bacteriophages—viruses that lyse particular bacteria—instead of antimicrobial drugs is still appealing for the treatment of diseases that are resistant to many drugs [33]. In several Eastern European nations, notably Georgia, phage therapy is still being utilized clinically today to treat bacterial infections that were initially discovered in the early 1920s. Phage therapy is becoming more and more well-liked as antibiotic resistance spreads throughout the world. A quick bactericidal medication acting on susceptible bacteria is comparable to the process of bacteriallysis by certain lytic phages. By adhering to surface receptors, phages spread intracellularly and break down the peptidoglycan cell wall of their bacterial host, so causing its destruction. Phage are found in many parts of nature and are consumed by millions of people every day [34]. For the treatment of multidrug-resistant disorders, the use of bacteriophages—viruses that lyse specific bacteria—instead of antimicrobial medications is tempting despite a number of drawbacks [33]. In many Eastern European nations, most notably Georgia, phage therapy is still being used clinically today to treat bacterial diseases, having been discovered in the early 1920s. With the global rise of antibiotic resistance, phage therapy is growing in popularity. A fast-acting bactericidal drug that targets vulnerable bacteria is similar to how some lytic phages cause bacteriallysis. Phages propagate intracellularly and destroy their bacterial host by breaking down the peptidoglycan cell wall through surface receptor adhesion. Phage are found in many parts of nature and are consumed by millions of people every day [34].

Antimicrobial Peptides

The cationic host defense peptides known as antimicrobial peptides (AMPs) are found in all kingdoms, including bacteria, fungi, plants, mammals, and protozoa. They have several methods of action. These medications act by interacting with the membrane and disrupting its bilayer structure rather than by targeting proteins in the bacterial cell. Host defense peptides, or HDPs, play crucial roles in the innate immune system. They regulate vital processes like immune cell chemokine release, wound healing promotion, immune cell anti-apoptotic activity, and adjuvant functions that increase the adaptive immune response [35]. For three main reasons, the concept of using these chemicals to target pathogenic bacteria raises hopes of preventing the emergence of antimicrobial medication resistance. First of all, because of their charged nature, which permits membrane rupture, AMPs function physically? Bacteria rarely reject this approach. Second, resistance is difficult to establish since a single peptide might have multiple modes of action based on its peptide structure, peptide-to-lipid ratio, and lipid membrane characteristics. It's difficult to develop resistance. Finally, because to developments in sequencing technology and molecular dynamics platforms, these tiny peptides can be readily changed and manufactured in silico to be employed as adjuvants to other antibiotics, increasing their effects and destroying any emerging resistance. To date, there have been many reports of AMP activity approaches. Kim et al., [36] conducted research on chicken NK (cNK) lysin, the chicken equivalent of human granulysin. Cytotoxic T cells and natural killer cells produce cNK, a cationic amphiphilic antimicrobial peptide (AMP), and its variants, such as the peptide cNK-2. They discovered that AMPs significantly affected both innate and adaptive responses. Site-directed mutation was used to determine the peptides' structure and function. In an attempt to chemically modify peptides, a group from Lanzhou University in China has experimented with conjugating fatty acid chains of different lengths. Through acetylation, cyclization, and other procedures, new and promising peptide compounds with antibacterial efficacy against a range of multidrug-resistant organisms were produced [37]. Several investigations have shown that adding dimers to AMPs influences both their increased activity and decreased toxicity (Malekkhaiat Häffner and Malmsten et al.,) [38]. Through their investigation, they demonstrated that peptide self-assembly (micelles, vesicles, nanofibers, nanotubes, etc.) had a better antibacterial activity. Zhu et al., created analogues of Mastoparan-C, an antibacterial peptide with outstanding broadspectrum action but a high potential for cell membrane rupture that endangers mammalian cells, in a separate study. It was discovered that the screened analogs were significantly less toxic and that they helped treat Gram-negative bacterial infections with Rifampicin and Gentamicin [39].

Nanoantibiotics

Nanoparticulate materials have the ability to store or distribute antibacterial chemicals. Metal and metal oxide-based nanoparticles and antibiotics are attractive therapeutic options for upcoming biological applications due to their low toxicity and improved antibacterial, antiviral, and anticancer action [40]. They have unique qualities because to their size, including as a higher surface area to volume ratio, which improves their compatibility, solubility, and simplicity of delivery and makes them superior drug carriers [41]. In addition to acting as carriers for particular drugs, nanoparticles can also demonstrate antibacterial properties of their own through a variety of mechanisms, including disruption of the bacterial wall, inhibition of biofilm formation, modulation of the host immune response, generation of reactive oxygen species, and damage to vital DNA and protein molecules of resistant bacteria [42]. Because of their various modes of action, nano-antibiotics are anticipated to be effective against bacteria that have developed antibiotic resistance. According to recent reports, bismuth nanoparticles have broad anticandidal activity and can stop the growth of drug-resistant strains of Candida auris in hospital settings [43]. However, additional in-depth research into the pharmacokinetics, specificity of action, and controllability of nanoantibiotics is required to guarantee their efficacy and safety in clinical settings.

Probiotics and Postbiotics

The identification of novel animal-origin probiotics and postbiotics—non-viable microbial probiotics or probiotic metabolites with biological activity in the host—may lead to improved dosage for enteric infections [44]. These probiotics and postbiotics can be combined with other therapies as an alternative. Bifidobacteria and lactic acid bacteria (LAB), which comprise species like Enterococcus, Lactobacillus, Lactococcus, Pediococcus, Vagococcus, Aerococcus, Carnobacterium, Streptococcus, and Weissella, are the two main families of lactic acid-producing microorganisms that make up probiotics. Probiotics can alternatively be called microbial feed supplements or living microorganisms. Since most LAB are thought to be benign, the presence of certain genera in the GI tract, mammary gland, and female genitourinary system is thought to be an alternate strategy for promoting health [45].

CRISPR-based Therapies

It has been determined that gene editing technologies, including the CRISPR-associated (CRISPR-Cas) system, are crucial tools in the fight against bacteria that are resistant to antibiotics. The systems' programmable nuclease protein (Cas) enables targeted and sequence-specific DNA cuts. These cuts are guided by guide RNA, which are RNA-based spacers flanked by partial repetitions. This technique has been applied as a sequence-specific treatment to target antibiotic resistance genes in pathogenic strains [46]. It sensitizes bacteria to antibiotics and inhibits the growth of plasmids carrying resistance genes. Three phases comprise the CRISPR-Cas system's functioning: adaptation, expression, and interference [47]. During the adaption step, the invaded DNA is incorporated into the host genome's CRISPR locus. During the expression stage, pre-crRNA expression and crRNA processing from the surrounding spacer sequences occur. Double strand breaks are brought about by the recognition of invasive DNA sequences by crRNA and the Cas proteins during the interference stage. Two classes—one with six types and 33 subtypes—of the CRISPR-Cas system are distinguished based on evolutionary links and molecular characteristics48. Class 2 features a single, large, multidomain Cas protein (Cas9, Cas12, Cas13, etc.) that binds to crRNA, while class 1 has many Cas proteins that mediate interference. Using CRISPR-Cas, antibiotic resistance can be addressed in several ways: (i) by directing Cas proteins to species-specific sequences, reducing the loss of normal microbiota; (ii) by telling the system to cleave drug-resistant genes, eliminating the bacteria harboring them and protecting the susceptible and wild ones; and (iii) by modifying or silencing resistance gene harboring plasmids to re-sensitize bacteria to antibiotics [49]. These diverse preclinical studies with CRISPR-Cas demonstrate the technology's potential for broad clinical adoption after thorough and open clinical assessment. Delivering this gene-editing tool to the bacterial system is the main challenge in developing it as an antibacterial drug. Combining bacteriophages is one way to boost the strategy's specificity [50]. Using CRISPR-Cas9 technology, virulence genes specific to S. aureus were removed from the genome of a temperate phage without sacrificing host specificity. The CRISPR-Cas9 antibacterial's selectivity against S. aureus was significantly enhanced as a result [51].

Antimicrobial Photodynamic Therapy

The fact that AMR makes previously successful medications ineffective against microbiological infections raises serious concerns for global public health. The growth of AMR necessitates the development of alternative therapeutic options for combating resistant microorganisms. Antimicrobial photodynamic treatment (aPDT) has emerged as a promising strategy to combating AMR, with distinct advantages. Antimicrobial photodynamic therapy uses a combination of photosensitizing drugs and light at precise wavelengths to cause microbial cell death. The process consists of three critical components: a photosensitizer, proper wavelength light, and molecular oxygen. Reactive oxygen species (ROS) are produced when the photosensitizer absorbs photons and transitions into an excited state, which transfers energy to the surrounding molecular oxygen. These ROS, which include free radicals and singlet oxygen, induce oxidative damage to microbial cells, ultimately leading to their death. Importantly, aPDT has broad-spectrum antibacterial action, attacking bacteria, fungi, and viruses without producing the resistance mechanisms seen with conventional antibiotics [52]. The increase of AMR has sparked interest in alternate therapeutic techniques, and aPDT provides various advantages in this setting. To begin, aPDT is effective against multidrug-resistant bacteria, especially those with substantial antibiotic resistance mechanisms. This is due to its non-specific mode of action, which works around traditional resistance mechanisms including efflux pumps and enzymatic degradation. Furthermore, aPDT can be adjusted to target specific microbial species or strains by selecting appropriate photosensitizers and light conditions, resulting in a more individualized treatment approach. Furthermore, aPDT can be used as an adjuvant therapy to conventional antibiotics, increasing their efficacy while lowering the likelihood of resistance development [53].

Combination Therapies and Personalized Medicine

The growing issue of AMR needs new techniques to fighting infectious illnesses. Combination therapy and tailored medicine have emerged as promising approaches to addressing AMR-related issues. This essay delves into the ideas, applications, problems, and future possibilities of combination therapy and customized medicine in the context of AMR [54]. Combination therapies entail using two or more antimicrobial drugs at the same time to improve efficacy and overcome resistance mechanisms. Combination treatments, which target numerous cellular pathways or biological targets, can boost antibacterial action while decreasing the likelihood of treatment failure. Additionally, combination medicines provide broad-spectrum coverage against a variety of infections, reducing the establishment of resistance and boosting therapeutic results. Furthermore, combining antimicrobial drugs with distinct modes of action can reduce cross-resistance and improve therapeutic efficiency, especially in multidrug-resistant diseases [55].

Personalized medicine comprises adapting treatment plans to individual patients based on genetic, clinical, and environmental factors. In the context of AMR, personalized medicine includes genotypic and phenotypic testing to guide therapy selection, taking into account pathogen susceptibility profiles and resistance mechanisms. Furthermore, customized medicine takes into account host characteristics such as immunological status, comorbidities, and pharmacogenetics to improve therapeutic outcomes while minimizing side effects. Precision antibiotic therapy, driven by pathogen-specific susceptibility data, allows for customized treatment regimens that improve clinical efficacy while lowering the risk of resistance and antibiotic-related comorbidities [56]. Table 2 summarizes the ideas of combination therapy and individualized medicine in fighting AMR.

Table 2: Concepts of combination therapies and personalized medicine in combating AMR

Concept	Description
Combination Therapies	• Treatment strategies that combine two or more medications to improve efficacy, reduce toxicity, prevent resistance, or target different elements of the infection. • **Enhance Efficacy:** The synergistic effects of combining medications may lead to better therapeutic outcomes. **Reduce Toxicity:** The synergistic effects of mixing drugs may result in greater therapeutic outcomes. • **Prevent Resistance:** Combining medications with various methods of action can reduce pathogen resistance. • **Target Different Aspects:** Drugs that target multiple stages of the infectious process can increase overall therapeutic efficacy.
Personalized Medicine	• Tailoring medical therapy to each patient's unique traits, including genetic makeup, life-style, and environmental circumstances. • **Genetic Makeup:** Understanding a patient's genetic propensity to infections and treat-ment reactions enables tailored therapeutic selection. • **Lifestyle Factors:** Patient lifestyle factors, including as nutrition and exercise, can in-fluence therapy effectiveness and susceptibility to infection. • **Environmental Factors:** Considering environmental factors, such as pathogen expo-sure, might help to influence treatment and preventative tactics.

Integration of Combination Therapies and Personalized Medicine

The use of combination therapy and tailored medicine shows great promise in addressing AMR. This method maximizes treatment efficacy while reducing the likelihood of resistance formation by combining various antimicrobial medicines tailored to individual patient and pathogen features. Genomic sequencing and quick diagnostic technologies make it easier to identify pathogen-specific resistance mechanisms, which can help guide the selection of appropriate combination medicines. Furthermore, the use of pharmacogenomic techniques allows for tailored dosing regimens that optimize therapeutic efficacy and safety profiles depending on individual patient characteristics [57].

Challenges and Future Directions

An effective strategy to tackle bacterial resistance is to combine non-antibiotic materials with antibiotics, as exemplified by the combination of amoxicillin and clavulanic acid, which inhibits β_-lactamase. This has led to an annual increase in the screening, discovery, and development of novel antibiotic and non-antibiotic synergy over the last ten years. In this review, we want to present a summary of the antibiotic synergistic routes and antimicrobial potentiators that address the existing mechanisms of resistance. We also discuss a wide range of potential antimicrobial potentiators, including phages, metabolites, metals and metal oxides, plant-derived active components, and AMPs, which can be used in conjunction with antibiotics to overcome resistance to present drugs. Through direct or indirect enhancement of their efficiency against resistant bacteria, these medications prolong the half-life of currently available antibiotics [58]. Antibiotic resistance is becoming more prevalent worldwide and is associated with increased morbidity and death in both clinical and community settings. Effective control strategies have been made more difficult by the appearance of superbugs and the spread of antibiotic resistance to diverse environmental niches. Strategies for preventing and controlling antibiotic resistance ought to be put into practice on a global, national, and local scale. Using antimicrobials rationally, controlling access to over-the-counter medications, improving hand hygiene, and optimizing infection prevention and control are among the main strategies that have been suggested. Along with innovation in new drugs, antibiotic delivery technologies, non-antibiotic substitutes, and vaccines, a full grasp of resistance mechanisms is necessary [59]. To combat antibiotic resistance, a coordinated, multidisciplinary, and regulatory approach is

needed. Adopting antibiotic resistance solutions is challenging and has wide-ranging effects. Although there have been proposals for remedies and some have already been started, not enough has been done to address the problem thus far.

All health care systems still need to use antibiotics, and it would be devastating if medical, social, and economic efforts were not coordinated. With medication resistance rising, simple antibiotic therapy is no longer an option. Clinical infection management approaches and treatments need to change in response to emerging therapeutics and epidemiological trends in multidrug-resistant bacteria. The adoption of novel research approaches for infection treatments, which comply with three criteria (i.e., the discovery of new treatments that are successful, the prevention of resistance, and the protection of the natural host microbiota), should hopefully be encouraged by ongoing emphasis. Creating novel combination tactics that integrate smart and local delivery technologies is the best way to achieve these goals.

Conclusion:

Antimicrobial resistance (AMR), which has been identified and is spreading quickly, is a major threat to public health worldwide since it reduces the effectiveness of current antibiotics and raises healthcare costs. Addressing this challenge requires novel approaches that go beyond standard antibiotic development. To tackle resistant infections, a variety of techniques are being investigated, including combination medicines, immunotherapy, phage therapy, and CRISPR-based therapeutics. Furthermore, the incorporation of personalized medicine holds promise for personalizing treatment regimens to particular patients and diseases, potentially reducing resistance development. However, combating AMR necessitates a concerted effort involving healthcare professionals, researchers, lawmakers, regulatory agencies, and the pharmaceutical sector. Working collaboratively, we can implement effective antimicrobial stewardship programs, promote infection prevention measures, and accelerate the discovery of innovative treatments to combat AMR and protect global public health.

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